REMARKS

I. Status of the claims

Claims 1, 14-16, 26, and 29-44 are pending. Claims 1, 14-16, 26 and 29-30 stand rejected. New claims 31-53 have been added. Claims 1, 14-16 and 26 have been amended. Claims 2-13, 17-25, and 27-28 have been cancelled. Applicants thank the Examiner for the helpful discussion of the pending claims and cited references during the office interview on June 25, 2008.

II. Claim Amendments

Claim 1 has been amended for clarity. For example, claim 1 has been amended to recite that the pulmonary infection is "associated with mucus or a bacterial biofilm." Support for this amendment can be found in Figure 1, which depicts the sputum/biofilm in a patient with cystic fibrosis. Furthermore, the specification explains that thick mucus and biofilms resulting from bacterial colonizations "create barriers to effectively targeting infections with antiinfectives. The present invention overcomes these barriers . . ." *Specification* at ¶4. The specification also explains that the method can be used to treat non-cystic fibrosis related infections. *Id.* at p. 5, ¶ 23.

Claim 1 has also been amended to replace the phrase "liposomal/complexed amikacin" with "liposomal amikacin formulation." Support for this amendment can be found, for example, at page 7, paragraph 32, of the specification, which describes liposomes, and page 12, paragraph 48.

Claim 1 has further been amended to recite that the liposome comprises amikacin and a lipid component, "wherein the lipid component consists essentially of a neutral phospholipid and a sterol." Support for this amendment can be found, for example, at page 6, paragraph 29, which describes the different types of lipids, including cationic lipids, and negatively charged lipids.

Additionally, eight of the formulations described in the specification were prepared from a neutral phospholipid and a sterol, e.g., DPPC/Chol and DPPC/DOPC/Chol.

The limitation that the dosing is from once a day to once a week has been deleted, and reintroduced in dependent claim 35. Additionally, based on the discussion with the Examiner, the limitation that the lipid to drug ratio is less than 2.5:1 has been deleted, and reintroduced in dependent claim 43.

Claims 14-16 and 26 have been amended merely for clarity and to correct grammatical errors.

New claim 31 recites that the neutral phospholipid is a phosphatidylcholine, while claim 32 recites a list a certain phosphatidylcholines, and claim 33 recites DPPC. Support for these new claims can be found at page 6, paragraph 29, which describes the different lipids that can be used in the liposomes, including those recited in the new claims. Additionally, page 7, paragraph 31 specifically discusses phosphatidylcholines, such as DPPC, and 8 of 19 formulations listed in the table on page 20 use DPPC or a combination of DPPC and DOPC as the neutral phospholipid.

New claims 34 and 35 recite that the sterol is cholesterol, which is supported at page 6, paragraph 29, and page 7, paragraph 31, as well as in many examples in the table on page 20 of the specification.

Claims 36-37 provide certain mole ratios of DPPC and cholesterol. Support for these ratios can be found in the table on page 20, where a range of different mole ratios were exemplified.

Claims 38 to 42 recite the frequency of administration, and are supported by the claims as originally filed as well as throughout the specification.

New claims 43 and 44 recite that the lipid to drug ratio is less than 2.5:1 by weight, or 1.0 or less. Support for these claims can be found at page 12, paragraph 49, as well as in the table of examples on page 20. Applicants note that "[w]ith respect to changing numerical range limitations, the analysis must take into account which ranges one skilled in the art would consider inherently supported by the discussion in the original disclosure." M.P.E.P. § 2163.05. Applicants submit that the range 1.0:1 or less is inherently supported by the specification. In *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976), the ranges described in the original specification included a range of "25%- 60%" and specific examples of "36%" and "50%." A new claim limitation of "between 35% and 60%" met the description requirement. Similarly, the limitation of 1.0:1 or less is supported by the application as filed since applicants have exemplified the ratio of 1.0:1. *Specification* at page 20, Table.

New claim 45 recites that the amikacin is amikacin sulfate. Support for this amendment can be found in the example on page 20 of the specification, which describes the use amikacin sulfate in preparing a formulation. New claims 46 to 53 depend from claim 45, but are otherwise similar to claims 29, 33-37 and 43-44. These new claims are, accordingly, supported by the specification for the above-stated reasons.

For all of the reasons set forth above, no new matter has been added by these amendments.

III. Declaration of Meers

The present claims are directed to a "method of treating a pulmonary infection associated with a mucus or a bacterial biofilm comprising administering to the lungs of the patient an effective amount of a liposomal amikacin formulation, which comprises amikacin and a lipid component, wherein said lipid component consists essentially of a sterol and a neutral phospholipid." *Amended claim 1*. One significant challenge to antibiotic therapy in treating lung infections, such as *P.*

aeruginosa infections, is the biofilm mode of growth. For example, aminoglycosides have slow penetration because of electrostatic interactions with the mucus and biofilm matrices. Furthermore, subinhibitory levels of aminoglycosides can actually induce biofilm formation. *Declaration of Meers, Exhibit A*, p. 860, column 1.

The present claims overcome these limitations by administering to the lungs a liposomal amikacin formulation, wherein the lipid component consists essentially of a neutral phospholipid and a sterol. Applicants provide herein evidence of unexpected results of the presently claimed method. *Declaration of Meers.* For example, the neutral phospholipid and sterol formulation has been shown to effectively penetrate bacterial biofilms and the sputum of cystic fibrosis patients It is believed that this enhanced penetration allows the amikacin to reach the bacteria. *Id.* at ¶ 8, *Exhibit A,* p. 860, col. 1-2. Liposomes containing cationic or anionic lipids, in contrast, do not penetrate the biofilm as effectively. For example, the liposomes containing at least some amount of a cationic lipid adhere to the negatively charged biofilm surface due to electrostatic interactions, *Id.* at ¶ 7, *Exhibit A*, at p. 866. Liposomes containing negatively charged lipids also fail to penetrate the biofilm as effectively as the neutral liposomes. It is believed that this is due to repulsion between to the negatively charged biofilm surface and negatively charged phospholipids. *Id.* at ¶8-10.

IV. Rejections Under 35 U.S.C. § 103(a)

A. Hersch or Profitt in view of Gonda or vice versa

The Examiner has rejected claims 1 and 5-30 as being unpatentable over U.S. Patent Application no. 5,756,120 to Hersch et al ("Hersch") or International Publication No. WO/9412155 to Profitt et al ("Profitt") in view of U.S. Publication No. 2005/0019926 to Gonda et al. ("Gonda") or vice versa. In order to establish a *prima facie* case of obviousness, the Examiner must determine the scope and content of the prior art, ascertain the differences between the claimed invention and the prior art and resolve the level of ordinary skill in the pertinent art. *Graham v. John Deere Co.*, 383 U.S. 1, 148 (1966). Once the Graham factual inquiries have been resolved, the Examiner must

explain why the differences between the cited references and the claims would have been obvious to one of ordinary skill in the art. Fed. Reg. Vol. 72, No. 195, p. 57527. The Supreme Court in *KSR* stressed that "obviousness cannot be sustained by mere conclusory statements; instead there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR* 127 S.Ct. 1727, 1740 (2007); see also Fed. Reg. Vol. 72, No. 195, p. 57529. "The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. Fed. Reg. Vol. 72, No. 195 at p. 57528. Additionally, objective evidence of nonobviousness must be considered. Such evidence, sometimes referred to as "secondary considerations," may include evidence of commercial success, long-felt but unsolved needs, failure of others, and unexpected results. *Id.*

Hersch describes liposomes containing a neutral lipid, a phosphatidylglycerol (i.e., a negatively charged lipid), cholesterol, and amikacin, where the drug to total lipid ratio is from 1:9 to 1:3. *Hersch* at col. 5, ll. 52-55. The Profitt disclosure is substantially identical or at least substantially similar to Hersch. Gonda describes compositions comprising nucleic acids complexed with a cationic aminoglycoside, where the nucleic acid is "condensed." *Gonda* at ¶ 9. The compositions of Gonda provide a "a means for introducing a nucleic acid and/or a gene product into a cell . . . ." *Id.* at ¶ 10. Nucleic acids condensed with polyvalent cationic species are less susceptible to degradation by nucleases. *Id.* at ¶ 28. In some embodiments, the cationic aminoglycoside-nucleic acid complex may be administered by inhalation. In certain embodiments of Gonda, the composition also may include one or more lipids or polymers. *Id.* at ¶ 57.

According to the Examiner, it would have been obvious "to administer the composition of Hersch or [Profitt] by aerosol delivery (pulmonary) since Gonda teaches that using this route of

administration for amino glycosides, one can achieve a deposition of the composition in the desired part of the respiratory tract." *Office Action* at p. 3-4. Applicants respectfully traverse.

As explained in the Declaration under 37 C.F.R. § 1.132 by Meers, attached hereto, Applicants have achieved unexpected results in administering a liposomal amikacin formulation, comprising amikacin and a lipid component, wherein the lipid component consists essentially of a neutral phospholipid and a sterol, as presently claimed. As explained in the specification at p. 1, ¶4 and Exhibit A of the Declaration of Meers, the mucus of cystic fibrosis patients and bacterial biofilms, such as those associated with a *P. aeruginosa* lung infection, make the treatment of such infections As noted in paragraph 6 of the declaration, neutral liposomes are able to significantly penetrate *Pseudomonas* biofilms. Experiments were conducted comparing the ability of neutral, positively charged, and negatively charged liposomes to penetrate a *Pseudomonas* biofilm. The results showed that the neutral liposome (DPPC/Chol) had significantly deeper penetration into the biofilm, and with higher concentration, compared to DPPC/DPPG/chol or DPPC/DPTP/Chol, in large biofilm patches with distinct boundaries. *Declaration of Meers* ¶ 10, Exhibits B and C. The clinical benefits seen in a Phase II clinical trial are attributed in part to this penetration capability. *Id* at ¶¶ 12-13, Exhibits D and E.

None of the cited references, taken alone or in any combination, teach or suggest that amikacin encapsulated in a neutral phospholipid-based liposome is capable of penetrating a biofilm or infected mucus, such as the mucus found in cystic fibrosis, bronchiectasis, or COPD patients, for example. Furthermore, none of the cited references, taken alone or in any combination, teach or suggest that amikacin encapsulated in a neutral phospholipid-based liposome would achieve the clinical benefits demonstrated by the aforementioned clinical results, such as a sustained increase in

FEV1, reduction in bacterial density, reduced frequency of exacerbation and hospitalization, significant weight gain, and improved CFQR-respiratory scale. For at least these reasons, Applicants request withdrawal of this rejection.

B. Gonda

The Examiner also has rejected claims 1 and 5-30 as being obvious over Gonda et al. The Examiner states that Gonda discloses liposomal formulations containing aminoglycosides, and that these formulations can given by pulmonary administration and be used to treat bacterial infections. Applicants respectfully traverse.

Gonda merely describes liposomes as one of many possible formulations of its nucleic acid-amino glycoside complexes. According to Gonda, the liposome should enhance transfection, and to this end, Gonda emphasizes cationic lipids, which fuse to the negatively charged surfaces of cells. *Gonda* at ¶¶ 57-61 and 64-66. Nothing in Gonda would lead the skilled artisan to select the instantly claimed neutral phospholipid and cholesterol. Indeed, Gonda's strong teaching of cationic liposomes would lead the skilled artisan away from the present invention.

A cationic liposome formulation was shown to bind to the surface of a biofilm. *Declaration of Meers,* Exhibits B and C. As explained above and in the Meers declaration, Applicants claimed method of administration of a liposomal formulation, where the lipid component consists essentially of a neutral phospholipid and a sterol, provides unexpected biofilm and mucus penetration, and accordingly, excellent clinical results. Gonda fails to teach or suggest that amikacin encapsulated in a neutral phospholipid-based liposome is capable of penetrating a biofilm or infected mucus. Furthermore, Gonda fails to teach or suggest that amikacin encapsulated in a neutral phospholipid-

based liposome would achieve the clinical benefits demonstrated by the aforementioned clinical results described in the Declaration of Meers.

Applicants further submit that the nucleic acids complexed with cationic aminoglycosides of Gonda would not provide a therapeutic antibiotic effect. Gonda seeks fusogenic liposomes, such as cationic liposomes, in order to promote transfection of the contents of the liposome into a cell. *Id.* at ¶57. Applicants submit that one of ordinary skill in the art would understand that the nucleic acid complexed with an aminoglycoside would not provide any antiinfective benefit to the patient. Transfection of the nucleic acid-aminoglycoside complex into the mammalian target cell renders the aminoglycoside unavailable to function effectively as an antibiotic against intracellular infections, which reside outside of the cells. As explained in Exhibit A, p. 860, "subinhibitory levels of aminoglycosides help to induce biofilm formation." Thus, attempted use of Gonda's formulation to treat lung infection would actually worsen the infection.

For the reasons set forth above, Applicants request withdrawal of this rejection.

C. Lagace in view of Deol or vice versa

The Examiner has rejected claims 1 and 5-30 as being unpatentable over U.S. Patent no. 5,662,929 to Lagace et al. ("Lagace") in view of Deol et al. "Lung specific stealth liposomes: stability, biodistribution and toxicity of liposomal antitubercular drugs in mice," Biochimica et Biophysica Acta 1334 (1997) 161-172 ("Deol") or vice versa. The Examiner notes that Lagace does not teach "inclusion of cholesterol in the liposomes." *Office Action* at p. 6. The Examiner relies on Deol for teaching "that cholesterol-containing liposomes are more stable." *Id.* Based on these teachings, the Examiner concludes that it would have been obvious to one of ordinary skill in the art to use cholesterol in the liposomes of Lagace. Applicants respectfully traverse.

The Lagace liposomes all comprise a negatively charged phospholipid and a neutral lipid. Specifically, Lagace explains "there is provided a low rigidity multilamellar liposomal formulation, free of cholesterol, comprising a neutral lipid an anionic lipid, and at least one therapeutic agent, wherein the liposomal formulation enhances the penetration of the therapeutic agent inside a bacterial cell." *Lagace* at col. 5, ll. 47-53 (emphasis added). Lagace further states that its liposomal formulation provides improved bactericidal activity in part because of the "original combination of phospholipids that markedly improve the penetration of a therapeutic agent in bacterial cells." *Id.* at col. 9, ll. 64-3. Thus, Lagace suggests that the inclusion of anionic lipids in the liposome is important for enhanced binding and penetration into bacterial cells.

Applicants claims, in contrast, administer a liposomal formulation comprising amikacin and a lipid component, which consists essentially of a neutral phospholipid and a sterol. As explained in the Meers declaration, the neutral phospholipid unexpectedly provides improved biofilm and mucus penetration in comparison to liposomes containing negatively charged lipids and accordingly, excellent clinical benefits, in stark contrast to Lagace's teachings.

Furthermore, Lagace strongly and repeatedly teaches *against* the use of sterols in the liposomes. A reference must be considered as a whole, including disclosures that teach away from the claimed invention. M.P.E.P. § 2142.02. Under *KSR*, "teaching away" still provides evidence of non-obviousness. *See* 127 S.Ct. at 1745. "[P]roceeding contrary to accepted wisdom in the art is evidence of nonobviousness." M.P.E.P. §2145 (citing *in re Hedges*, 783 F.2d 1083 (Fed. Cir. 1986)).

The Examiner contends that "if a minute amount of rigidity [] in Lagace's liposomes is desired one of ordinary skill in the art would be motivated to use such small amount based on the teachings of Deol. *Office Action* at p. 7. Applicants disagree.

Lagace's teachings against a sterol are clear and unequivocal. According to Lagace, "in order to maintain the desired characteristic of the liposome formulation, a low rigidity of the liposomes seems required." *Id.* at col. 10, l. 67 to col. 11, l. 5. Lagace also states that an aspect of the invention is "a low rigidity multilamellar liposomal formulation free of cholesterol." *Id.* at column 5, ll. 49-50. Lagace specifically points out that "the addition of cholesterol to the formulation described in Table 1 brought the Tc to a minimum value of 60° C. Such formulations were incompatible with modulation of gradual antibiotic liberation and suitable interactions with bacteria." *Lagace* at col. 10, ll. 63-66.

For all of the aforementioned reasons, Applicants respectfully request withdrawal of this rejection.

D. Lagace in view of Hersch

The Examiner also rejects the claims over Lagace in view of Hersch. The Examiner states that Lagace teaches encapsulation of aminoglycosides in liposomes for the treatment of *P. aeruginosa*, and relies Hersch for "show[ing] the routine use of cholesterol in liposomes." *Office Action* at p. 7. Thus, the Examiner concludes that the use of cholesterol in the liposomes of Lagace would have been obvious "since Hersch shows the routine use of cholesterol in liposomes for the treatment of infections." Applicants respectfully traverse.

Lagace and Hersch both include negatively charged phospholipids in their formulations, in contrast to Applicants claims, wherein the lipid component consists essentially of a neutral

phospholipid and a sterol. As explained above and in the Meers declaration, Applicants have achieved unexpected biofilm penetration and clinical benefit using a liposomal formulation, where the lipid component consists essentially of a neutral phospholipid and a sterol, and accordingly, excellent clinical results.

Additionally, as explained above, Lagace repeatedly teaches against the use of a sterol. Thus, the skilled artisan would not be motivated to incorporate a sterol in the liposomes of Lagace.

For at least these reasons, Applicants request withdrawal of this rejection.

V. Double Patenting

Claims 1-30 stand rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 74-76, 78-84, 86-87, 94-95, 98-102 and 105-108 of copending Application Serial No. 10/383,173 ("the '173 application"), either alone or in combination with Lagace. Applicants respectfully request that the Examiner hold in abeyance all obviousness-type double patenting rejections based on the '173 application until allowable subject matter is indicated.

VI. Conclusion

In light of the amendments and remarks set forth above, Applicants submit that the pending claims are in condition for allowance. Reconsideration and timely allowance of the pending claims is respectfully solicited. If a telephone conference would be helpful, the Examiner is invited to call the undersigned at 617-832-1223. Applicants hereby request that any additional fees required for timely consideration of this application be charged to **Deposit Account No. 06-1448, Reference TRA-008.01**

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